Is Obsessive-Compulsive Disorder Caused by a Second-Messenger Imbalance?

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ABSTRACT

Although the precise etiologic nature of obsessive-compulsive disorder (OCD), one of the most common psychiatric conditions, is unknown, several findings indicate involvement of the serotonin (5-HT) transporter. Apart from the specific effects of selective 5-HT reuptake inhibitors, other studies show decreased functionality of the platelet 5-HT transporter in OCD. In this report, the authors combine data from two independent studies of patients with OCD, showing both an increased activity of protein kinase type C (PKC) and a decreased activity of protein kinase type A (PKA). The authors propose a unifying hypothesis that OCD might be determined by an imbalance between PKC and PKA, with a prevalence of the former and, more generally, of the phosphoinositide over the cyclic adenosine monophosphate (cAMP) pathway. Should this hypothesis prove correct, the path would be open for new therapeutic interventions in the treatment of OCD.

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INTRODUCTION

Obsessive-compulsive disorder (OCD) is a psychiatric condition characterized by the presence of obsessions or compulsions, or both. Obsessions are defined as recurrent and persistent thoughts, impulses, or images that are experienced in an intrusive and inappropriate way, at some time during the disorder, which cause marked anxiety and distress and which persist despite all attempts to try to ignore, suppress, or neutralize them. Compulsions are defined as repetitive behaviors or mental acts that a person feels driven to perform in response to an obsession or according to rigid rules; such behaviors are aimed at preventing or reducing distress or a dreaded event and are always unrealistic or excessive. Although the sufferer generally recognizes that the obsessions or compulsions are products of his or her own mind, the degree of insight can vary, and a subtype with poor insight has been recognized.[1]

THE SEROTONIN TRANSPORTER IN OCD

Once considered rare and resistant to treatment, OCD recently has emerged as one the most common psychiatric conditions, with a lifetime prevalence of approximately 2.5%. Its treatment has changed dramatically over the last decade, following the introduction of selective serotonin (5-HT) reuptake inhibitors (SSRIs) that provide symptom remission in about 60% of patients.[2] The specific response of OCD patients to SSRIs has emphasized the possible role of the main target of these drugs, namely the 5-HT transporter, in the pathophysiology of the disorder. Research in this area has been assisted by the presence of a sodium- and temperature-dependent 5-HT transporter in blood platelets which shows striking similarities to that present in the central nervous system,[3] even though the blood cells are exposed to a different environment, including circulating hormones and neurotransmitters. Most results of OCD studies have been consistent and have shown decreased functionality of this structure in comparison to healthy control subjects, evaluated by direct measurement of 5-HT reuptake, of tritiated imipramine binding sites and, more recently, of tritiated paroxetine binding sites corresponding to the transporter protein itself.[4]

PROTEIN KINASE ACTIVITY

Little is known about intracellular regulation of the 5-HT transporter; however, the rapid changes in its activity and surface density have been linked to changes in the phosphorylation state. Recent data have demonstrated that the 5-HT transporter presents six phopshorylation sites: three for protein kinase type C (PKC) and three for protein kinase type A (PKA).[5] PKC is a class of phosphorylases present at a high level of concentration in the brain; diacylglycerol derived from the hydrolysis of phosphatidylinositol-4,5-bisphosphate (PIP2) stimulates PKC by increasing its affinity for calcium and membrane phospholipids, thus promoting its translocation from the cytosol to the particulate fraction.[6] On the other hand, PKA is stimulated by cyclic adenosine monophosphate (cAMP). The administration of phorbol esthers that activate PKC provokes a decrease in 5-HT reuptake, whereas choleric toxin (or a compound that similarly increases the cAMP concentrations and therefore PKA) increases 5-HT reuptake. Therefore, PKC inhibits and PKA activates 5-HT reuptake.[7]

We have recently demonstrated that, after activation of PKC, the velocity of reuptake decreased significantly in 15 untreated OCD patients (including both males and females) and in a similar group of control subjects. However, the decrease was more significant in the OCD patients (90% vs 80%); this suggests that PKC is hyperactive in OCD.[8] Hyperactivity of PKC also might explain the lower reuptake baseline values frequently reported for OCD patients. In turn, the hyperactivation of PKC might reflect increased endogenous production of diacylglycerol as a result of a hyperactive phosphatidylinositol (PI) pathway.

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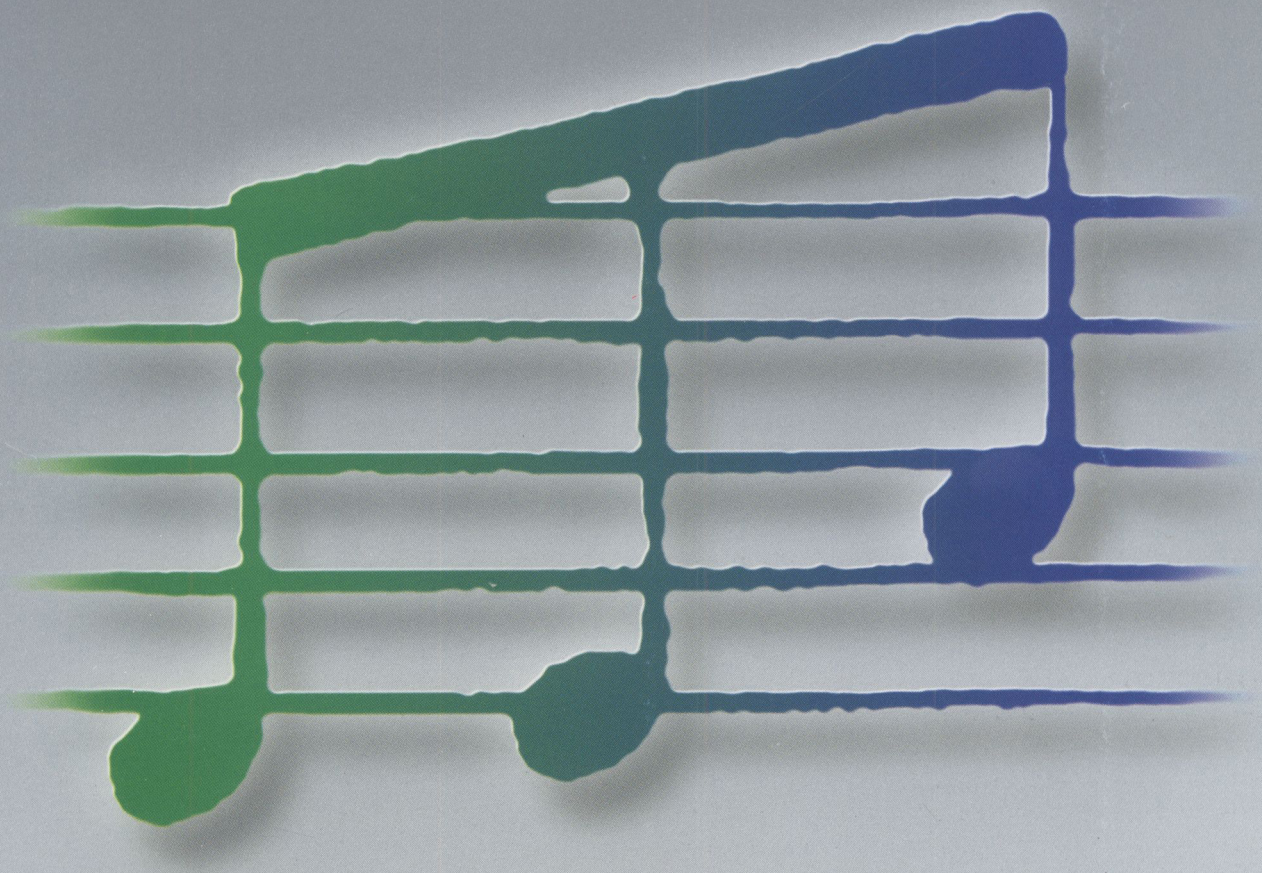

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Alternatively, a hyperactive PI pathyway and PKC may result from (or provoke) a condition of hypoactivity of the counterpart (ie, cAMP and, ultimately, PKA). Recent data are consistent with this suggestion. Some researchers,[9] using immunoblotting, demonstrated that while the regulatory subunits type I and II were increased, the catalytic subunit of PKA was decreased. Their study group, 12 drug-free OCD patients, also had lower cAMP-stimulated PKA activity.

A NEW BIOLOGICAL HYPOTHESIS OF OCD

On the basis of these convergent data, we suggest that OCD may be caused by an imbalance of the two main transductory pathways (cAMP and PI), with a prevalence of the second and a consequently higher activation of PKC (relative to that of PKA), given the cross-talk between the two main second messengers at the level of different effectors. Stimulation of the PI pathway in OCD is consistent with data showing a worsening of OCD symptoms after the administration of meta-chlorophenylpiperazine,[10] a nonspecific 5-HT_{2C} receptor agonist, and it is well known that 5-HT_{2C} receptors are linked to G protein-activating phospholipase C, which initiates the breakdown of PI.

Abnormalities in PKC and PKA and some of their substrates have been found in peripheral cells and in the brains of patients with affective disorders.[11] These observations, together with our combined data, may delineate an emerging explanation of the substantial comorbidity among such disorders.

CONCLUSIONS

Our data, evaluated as a whole, represent the first evidence of abnormal intracellular mechanisms in OCD, particularly PKC hyperactivity and PKA hypoactivity. The mechanisms leading to these conditions are not yet known, and currently they can be considered primary or secondary phenomena. Although our findings were obtained from two different groups of patients, and therefore require replication in the same patients for more reliable analysis, they nonetheless indicate possible new approaches to studying the pathophysiology of OCD (and possibly that of other psychiatric disorders) and suggest potentially new therapeutic strategies. CNS

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